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Kindly add new claims 60-62, as follows:

- 30  
60. (New) The method of claim <sup>29</sup>59, wherein the CNS neural stem cells, in the presence of differentiation-inducing conditions or an appropriate tissue environment, produce progeny cells that differentiate into neurons, astrocytes, and oligodendrocytes.
- 3  
61. (New) The composition of claim 60, wherein said differentiation-inducing conditions are *in vitro*.
62. (New) The composition of claim 60, wherein said differentiation-inducing conditions are *in vivo*.

#### REMARKS

Claims 26-27, 32-37, and 39-59 are pending in this application. These claims are directed to methods for transplanting CNS neural stem cell progeny to a host. Applicants have amended claims 26 and 40 to obviate the 35 U.S.C. § 112, second paragraph, rejections. These amendments add no new matter and are fully supported by the specification as filed.

Applicants have also added new claims 60-62. New dependent claim 60 recites a method of transplantation using an *in vitro* neural stem cell culture containing cells that can in the presence of differentiation-inducing conditions or an appropriate tissue environment, produce progeny cells that differentiate into neurons, astrocytes, and oligodendrocytes. This claim is supported in the specification and in the original claims (*see, e.g.*, pg. 16, lines 18 - 24; pg. 24, line 23 to pg. 29, line 5). Specific support for new claims 61-62 is found in specification, pg. 16, lines 24-29. These claims add no new matter.

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### THE § 112, FIRST PARAGRAPH REJECTION

The Examiner has rejected claims 26, 27, 32-37 and 39-59 under 35 U.S.C. § 112, first paragraph, alleging that the claims are not enabled for a therapeutic treatment. Applicants traverse.

First, the claims recite a method of transplanting CNS neural stem cell cultures to a host, whether for non-therapeutic or therapeutic uses. "Any analysis of claims for compliance with 35 U.S.C. 112 must begin with an analysis of the claims to determine exactly what subject matter they encompass. The subject matter there set out must be presumed, in the absence of evidence to the contrary, to be that which the applicant regards as his invention." *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). By alleging that these claims are not enabled for therapeutic treatment, the Examiner improperly reads limitations from the specification into the claims. "The claim, not the specification, measures the invention." *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 597 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984).

Second, Applicants have provided overwhelming evidence of record that demonstrates enablement of the claimed methods for transplantation of CNS neural stem cells. The CNS neural stem cells of the invention are a strikingly useful source of transplantable neural tissue. Because CNS neural stem cells can be cultured *in vitro*, and are self-renewing, multipotent, and capable of differentiating to a variety of desirable cell types depending upon culture conditions or tissue environment, neural transplantation using the cells of the invention is facilitated, compared to prior art transplantation methods, as noted in the specification, pg. 11, lines 15-20:

"The inability in the prior art of the transplant to fully integrate into the host tissue, and the lack of availability of cells in unlimited amounts from a reliable source for grafting are, perhaps, the greatest limitations of neurotransplantation. It would be more preferable to have a well-defined, reproducible source of neural tissue for transplantation that is available in unlimited amounts."

One skilled in the neurobiological art could, at the date of filing, have readily transplanted the CNS neural stem cells of the invention into a host, without undue experimentation, by using the specification as a guide. The specification provides ample guidance as to how to transplant

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CNS neural stem cells (*see*, specification, pg. 36, line 10, to pg. 42, line 13; pg. 68, line 16, to pg. 69, line 18; pg. 78, line 17, to pg. 71, line 6; pg. 96, line 12, to pg. 97, line 28). The specification also teaches that following transplantation, the CNS neural stem cells differentiate to various cell types appropriate to the tissue into which the CNS neural stem cells are transplanted (*see*, specification, pg. 69, line 19, to pg. 70, line 7; pg. 97, line 29, to pg. 103, line 14). The prior art had taught methods of transplantation (*see*, specification, pg. 6, line 19, to pg. 11, line 12), although none of the prior art taught or could have taught the claimed transplantation of the CNS neural stem cells of the invention.

The *nature of the invention* is such that the transplantation of CNS neural stem cells can be readily verified (*see*, specification, pg. 71, line 26, to pg. 72, line 16; pg. 73, lines 4-30). The transplantation methods of the invention were well within the abilities of one of skill in the art, as shown by the voluminous evidence, subsequently produced by Applicants and by other neurobiologists, that the CNS neural stem cells of the can be transplanted to a host and that following transplantation, the CNS neural stem cells differentiate, in the appropriate tissues conditions, to important and useful cell types. Among the evidence for enablement of the claims are the following:

*The specification teaches a non-therapeutic transplantation utility and provides working examples of actual transplantation.*

The Examiner acknowledges (Paper 29, pg. 3, para. 3) that the specification teaches and provides working examples for the actual transplantation of CNS neural stem cells into a host. The Examiner also acknowledges that these CNS neural stem cells survive this transplantation.

The Examiner further acknowledges that transformed CNS neural stem cells transplanted into a host produce  $\beta$ -galactosidase in the host (thereby providing the non-therapeutic utility of determining neural development events, *see*, specification, pg. 78, Example 27, *citing*, Walsh & Cepko, 241 Science 1342).

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*The specification teaches and provides working examples of transplantation and remyelination.*

The Examiner acknowledges that CNS neural stem cell progeny can initiate remyelination. Patches of myelin were found in the dorsal columns of the spinal cord of the recipients of both rat and mouse cells (*see*, specification, pg. 69, line 22, to pg. 70, line 7). Because remyelination can begin only after transplantation, the specification must therefore enable transplanting CNS neural stem cells to a host.

The specification teaches that transplantation, followed by partial remyelination, is useful (*see*, specification, pg. 42, lines 9-13, "It should also be borne in mind that in some circumstances remyelination by precursor cells will not result in permanent remyelination, and repeated injections will be required. Such therapeutic approaches offer advantage over leaving the condition untreated and may spare the recipient's life.")

*The Declaration under 37 C.F.R. § 1.132 of Hammang in United States patent application 07/961,813 provides evidence for transplantation and remyelination.*

Enclosed with this amendment is a Declaration under 37 C.F.R. § 1.132 that had been submitted in an applications from which the present application claims priority, the Declaration by Dr. Joseph P. Hammang, in United States patent application 07/961,813 (*see*, attached Exhibit 1). In paragraph 4 of his declaration, Dr. Hammang declares that the "precursor cells [*i.e.*, CNS neural stem cells] can be harvested and transplanted into a myelin-deficient recipient wherein the precursor cells can differentiate into oligodendrocytes and remyelinate the axons of the recipient." This Declaration is also evidence for the enablement of CNS stem cell transplantation.

*The Declaration under 37 C.F.R. § 1.132 of Hammang in United States patent application 08/479,796 also provides evidence for transplantation and remyelination.*

Enclosed with this amendment is a Declaration under 37 C.F.R. § 1.132 that had been submitted in co-pending application United States patent application 08/479,796, which has a specification identical to the present application (*see*, attached Exhibit 2). The Declaration

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provides additional evidence of remyelination in rodents and dogs (*see*, Declaration, para. 11-30). These data are also evidence for the enablement of CNS stem cell transplantation.

*The state of the art at the time of filing supported neural cell transplantation generally, as shown by the McKay review article.*

The state of the art at the time of filing was such that transplantation of neural cells generally was enabled. The Examiner cites McKay, 276 Science 66-71 (1997) ("*McKay*") (*see*, attached Exhibit 3) for the statement that "clinical trials show that neuron replacement therapies for neurodegenerative diseases, such as Parkinson's and Huntington's disease, are feasible." (McKay, pg. 70, col. 2, lines 14-17). *McKay* further teaches that transplantation of CNS neural stem cells into a host had been done by 1997, using methods similar to the methods described in the specification (*see*, the many references in *McKay*). Note that *McKay* cites the inventors, Reynolds and Weiss, and much of their subsequent work with CNS neural stem cells (*see, e.g., McKay*, p. 67, right column).

*The Applicants have shown transplantation of both mouse and human CNS neural stem cell using the methods of the invention and have published these transplantation results in several scientific journals.*

The named inventors and their co-workers have published numerous papers reporting results of transplantation of CNS neural stem cells. Drs. Reynolds and Weiss (named inventors) subsequently reported that the CNS neural stem cells of the invention have self-renewing properties; divide in an asymmetric fashion (divide to produce an identical stem cell and a more differentiated daughter cell); and are capable of giving rise to neuronal and glial cells throughout the life span of the animal. Reynolds & Weiss, 255 Science 1707-1710 (1992) ("*Reynolds & Weiss*") (submitted in the Information Disclosure Statement of May 23, 1997; reference 66). *Reynolds & Weiss* specifically mentions the use of CNS neural stem cells in experimental and therapeutic transplantation (*see, Reynolds & Weiss*, pg. 1709, right column).

Applicants also reported the ability to generate expandable cell cultures according to the claimed invention from embryonic mammalian CNS tissue. Reynolds *et al.*, 12 J Neurosci. 4565-

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4574 (1992) ("*Reynolds et al.*") (submitted in the Information Disclosure Statement of May 23, 1997; reference 64). Subsequent authors have generally acknowledged Weiss and Reynolds as the first refer to report CNS stem cells, as claimed in the methods of the invention.

In his 1993 review, Dr. Baetge, also a named inventor (695 Ann N.Y. Acad. Sci. 285-291 (1993) ("*Baetge*") (attached as Exhibit 4)) reviews the desired qualities of an "ideal" cell for nervous system transplantation. *Baetge* indicates that CNS neural stem cells possess these ideal qualities, since they can be expanded to form large quantities of cells, they are non-immortalized and thus non-tumorigenic, and capable of differentiating into neurons and glia (*see, e.g., Baetge, p. 286*). *Baetge* goes on to review *Reynolds & Weiss* and *Reynolds et al.* *Baetge* concludes "from the work by Reynolds and Weiss that the EGF-responsive cells have self-renewing properties ... and divide in an asymmetric fashion (divide to produce an identical stem cell and a more differentiated daughter cell) and are capable of giving rise to neuronal and glial cells throughout the life span of the organism." *Baetge, p. 288, left column*. In sum, *Baetge* confirms the transplantable characteristics of CNS neural stem cell and confirms that the claimed method is a pioneering advance.

In 1994, Dr. Hammang (another named inventor) and co-workers reported several methods of transplanting CNS neural stem cells and the results of those transplantations. *See, Hammang et al., in 21 Methods in Neurosciences, 281-293 (Flanagan et al., eds., Academic Press, San Diego, 1994) ("Hammang I") (attached as Exhibit 5)*. *Hammang I* discloses the formation of myelinating oligodendrocytes *in vivo* from transplanted CNS neural stem cells, as well as the formation of various neural cell progeny from transplanted CNS neural stem cells that carry the genetic marker *lacZ*.

Applicants and coworkers further characterized their neural stem cell cultures in Weiss *et al., 16 J. Neurosci. 7599-7609 (1996) ("Weiss et al.") (attached as Exhibit 7)*. *Weiss et al.* reported that neural stem cells according to the claim invention could also be isolated from the adult mammalian spinal cord and the ventricular neuroaxis. EGF and bFGF cooperated to induce the proliferation, self-renewal, and expansion of these neural stem cell cultures (*i.e., the neural*

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stem cell cultures of the invention). The proliferating neural stem cells cultures, in both primary culture and secondary expanded clonal cultures, could be expanded or proliferated as undifferentiated cultures, and could be induced to differentiate into neurons, astrocytes, and oligodendrocytes under suitable culture conditions.

Additional evidence shows that when the undifferentiated CNS neural stem cells are injected into the myelin-deficient rat spinal cord, they respond to endogenous cues within the mutant CNS and differentiate into myelinating oligodendrocytes. Hammang *et al.*, 147(1) Exp Neurol. 84-95 (1997) (*Hammang II*) (attached as Exhibit 9). This behavior is in contrast to their behavior *in vitro*, where CNS neural stem cells mainly form astrocytes. *Hammang II* shows that, because CNS neural stem cells “are influenced to divide using growth factors, rather than oncogenes, and because they appear to make appropriate lineage decisions when transplanted into a mutant environment, they may provide an excellent source of cells for a variety of future therapies using cellular transplantation.” (see, *Hammang II*, Abstract).

*Others skilled in the art have confirmed the suitability for transplantation of human CNS neural stem cells.*

CNS neural stem cells were further characterized, using human neural stem cell cultures, in Cattaneo *et al.*, 42 Mol. Brain Res. 161-66 (1996) (“*Cattaneo*”) (attached as Exhibit 6). *Cattaneo* cites Reynolds & Weiss (p. 162, left column). *Cattaneo* goes on to show that multipotent human CNS neural stem cell cultures have been serially subcultured and expanded in serum-free growth medium containing EGF, and when grown in suspension culture, form “neurosphere” aggregates of variable sizes. As *Cattaneo* notes, the human neural stem cell cultures, like their rodent and canine homologues, are capable of differentiating into neurons, astrocytes, and oligodendrocytes when differentiated by removal of the growth factor mitogen from the culture medium (see, *Cattaneo*, p. 162, left column). *Cattaneo* refers to human CNS neural stem cells as “a plentiful source of neurons and glia suitable for transplantation.” (see, *Cattaneo*, pg. 165, left column.).

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Others skilled in the art have used the methods of this invention to show that transplantation of canine CNS neural stem cells and results in remyelination in dogs.

Milward *et al.*, 50 J. Neurosci. Res. 862-871 (1997) ("Milward") (attached as Exhibit 8) successfully transplanted canine CNS neural stem cells both into rat and into a shaking (sh) pup myelin mutant dog (a model of human myelin diseases). Canine CNS neural stem cell clusters, similar in appearance to murine neurospheres, were obtained from canine brain and expanded *in vitro* in the presence of EGF for at least 6 months. Transplantation of *lacZ*-expressing canine neurospheres into the myelin-deficient (md) rat showed that a proportion of the cells differentiated into oligodendrocytes and produced myelin. In addition, cells from the neurosphere populations survived at least 6 weeks after grafting into a 14-day postnatal sh pup recipient and at least 2 weeks after grafting into an adult sh pup recipient. Thus, *Milward* showed that CNS neural stem cells provide a source of allogeneic donor cells for transplantation studies.

Others skilled in the art have used the claimed methods of this invention to show transplantation of mouse CNS neural stem cells and incorporation of differentiated glial cells in rat brains.

Using an *in utero* xenotransplantation approach, Winkler *et al.*, 11(3) Mol. Cell. Neurosci. 99-116 (1998) ("Winkler") (attached as Exhibit 10) examined the developmental potential of mouse CNS neural stem cells that had been injected into the E15 rat forebrain ventricle. *Winkler* established cell cultures from control mice or from mice carrying the *lacZ* transgene under control of the promoters for nestin, glial fibrillary acidic protein (GFAP), or myelin basic protein (MBP). The transplanted CNS neural stem cells displayed widespread incorporation into distinct forebrain and midbrain structures and differentiated into neurons, astrocytes, and oligodendrocytes (*see, especially, Winkler, Fig. 1*). *Winkler* showed that CNS neural stem cells can respond to host derived environmental cues, differentiate into cells with neuronal and glial-like features, and become integrated in the developing recipient brain.



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*Others skilled in the art have used the claimed methods of this invention to show therapeutically effective transplantation of human CNS neural stem cells into mice.*

Zigova & Sanberg, 16 Nature Biotechnol. 1007-1008 (1998) ("*Zigova & Sanberg*") (attached as Exhibit 11) is a scientific news article that critically reviews both the results of *Flax* (below) and the results of *Brüstle* (below) Both *Flax* and *Brüstle* provide proof that, using methods provided in the specification, human CNS neural stem cells can, using the appropriate *in vivo* developmental cues, can differentiate to functional neural cells, even in a mouse brain.

Flax *et al.*, 16 Nature Biotechnol. 1033-1039 (1998) ("*Flax*") describes the transplantation of human neural stem cells into mice to replace deficient mouse neuronal populations (Exhibit 12). Using methods that are substantially the same as those provided in the specification, *Flax* "provides strong evidence that the NSCs [neural stem cells] are able to perform *in vivo* and *in vivo* all the critical functions previously described for their rodent counterparts" (Zigova & Sanberg, pg. 1007, middle column).

Brüstle *et al.*, 16 Nature Biotechnol. 1040-1044 (1998) ("*Brüstle*") describes the implantation of fetal human brain cells into mice (Exhibit 13). Using methods similar to the those provided in the present specification, *Brüstle* transplanted human CNS progenitor cells into mice that "acquire an oligodendroglial phenotype and participate in the myelination of host axons" (Zigova & Sanberg, pg. 1008, right column).

*Others skilled in the art have used the claimed methods of the invention to show transplantation of rat CNS neural stem cells results in "robust myelination" using the methods of the invention.*

Applicants enclose herewith additional work from Dr. Duncan's lab (the work reported in *Milward* was also performed in Dr. Duncan's lab). See, Zhang *et al*, 96 Proc. Natl. Acad. Sci. USA 4089-94 (1999) ("*Zhang*"; attached hereto as Exhibit 14) In *Zhang*, neural stem cell cultures were generated from both juvenile and adult rats and used to produce myelin-forming cells, and when transplanted into *md* rats, those cells produced "robust myelination".

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*Others skilled in the art have used the claimed methods of the invention to show that transplantation of CNS neural stem cells results in "global" cell replacement and therapeutically effective remyelination in mice.*

The oligodendrocytes of the dysmyelinated shiverer (*shi*) mouse are "globally" dysfunctional because they lack myelin basic protein (MBP) essential for effective myelination. Therapy, therefore, requires widespread replacement with MBP-expressing oligodendrocytes. Yandava *et al.*, 96(12) Proc. Natl. Acad. Sci. 7029-34 (1999) ("*Yandava*"; attached hereto as Example 15) showed that clonal neural stem cells transplanted at birth-using a simple intracerebroventricular implantation technique-resulted in widespread engraftment throughout the *shi* brain with repletion of MBP. Accordingly, of the many donor cells that differentiated into oligodendroglia-there appeared to be a shift in the fate of these multipotent cells toward an oligodendroglial fate-a subgroup myelinated up to 52% (mean = approximately 40%) of host neuronal processes with better compacted myelin of a thickness and periodicity more closely approximating normal. *Yandava* showed that a number of recipient animals evinced decrement in their symptomatic tremor. *Yandava* suggest that "global" neural cell replacement is feasible for some CNS pathologies when cells with stem-like features are used.

*Others skilled in the art have used the claimed methods of the invention to show that transplantation of CNS neural stem cells results in site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain.*

Fricker *et al.*, 19 J. Neurosci. 5990-6005 (1999) ("*Fricker*"; attached hereto as Exhibit 16) obtained CNS neural stem cells from the embryonic human forebrain. These cells were expanded up to  $10^7$  fold in culture in the presence of epidermal growth factor, basic fibroblast growth factor, and leukemia inhibitory growth factor. When transplanted into neurogenic regions in the adult rat brain, the subventricular zone, and hippocampus, the *in vitro* propagated cells migrated specifically along the routes normally taken by the endogenous neuronal precursors: along the rostral migratory stream to the olfactory bulb and within the subgranular zone in the dentate gyrus, and exhibited site-specific neuronal differentiation in the granular and

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periglomerular layers of the bulb and in the dentate granular cell layer. The CNS neural stem cells exhibited substantial migration also within the non-neurogenic region, the striatum, in a seemingly non-directed manner up to approximately 1-1.5 mm from the graft core, and showed differentiation into both neuronal and glial phenotypes. Only cells with glial-like features migrated over longer distances within the mature striatum, whereas the cells expressing neuronal phenotypes remained close to the implantation site. *Fricker* showed the ability of the human neural stem cells to respond *in vivo* to guidance cues and signals that can direct their differentiation along multiple phenotypic pathways. *Fricker also* suggested that these cells can provide a powerful and virtually unlimited source of cells for experimental and clinical transplantation.

In summary, the specification enables the claims for the “method of transplanting CNS neural stem cell progeny to a host comprising: transplanting one or more central nervous system (CNS) neural stem cells to said host.” One of ordinary skill in the neurobiological art could readily have, at the filing date, transplanted the claimed CNS neural stem cells into a host without undue experimentation. The attached publications which use the claimed methods of this invention to transplant CNS neural stem cells provide overwhelming evidence of record that the instant invention is enabled. Applicants request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

#### **THE § 112, SECOND PARAGRAPH, REJECTION**

The Examiner has rejected claims 34 and 40 under 35 U.S.C. § 112, second paragraph, alleging that the claims are indefinite. The Examiner has suggested phrasing that would overcome these rejections. To advance prosecution, Applicants have amended claim 34 to recite “acidic fibroblast growth factor, basic fibroblast growth factor, and combinations thereof.” Applicants have amended claim 40 to conform more closely with claim 26. Claim 40 recites differentiated neural cells are selected from the group consisting of neurons and glia.

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The rejections under 35 U.S.C. § 112, second paragraph, are thus moot. Applicants request that the rejections be withdrawn.

### **THE § 102(b) REJECTION**

The Examiner has rejected claim 40 under 35 U.S.C. § 102 as being anticipated by *Cattaneo & McKay*, 347 Nature 762-65 (1990) ("*Cattaneo & McKay*").

Applicants have amended claim 40 to recite that differentiated neural cells are selected from the group consisting of neurons and glia. *Cattaneo & McKay* does not disclose CNS neural stem cell progeny, as recited in the claims. The *Cattaneo & McKay* cells are not multipotent, and do not self-renew. Rather, *Cattaneo & McKay* discloses NGF-responsive "neuronal precursor cells." The specification shows that neuronal precursor cells are not stem cells (*see*, specification, pg. 14, lines 1-10; pg. 20, lines 3-11). The term "neuronal" is well understood by the art to define cells that are committed to differentiate into neurons, but not into glial cells such as oligodendrocytes or astrocytes. *Cattaneo & McKay* itself makes this crystal clear (*see, e.g.*, abstract, p. 762: "the proliferative cells differentiate into neurons").

The amendments to claim 40 have thus rendered the rejection under 35 U.S.C. § 102(b) as moot. Applicants request that the rejection be withdrawn.

### **THE PROVISIONAL OBVIOUS-TYPE DOUBLE PATENTING REJECTION**

The Examiner has provisionally rejected claims 26, 32-35 and 40-58 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 16-18, 32-33, 36, 41-43 and 72 of co-pending application United States patent application 08/479,796. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Applicants traverse this rejection.

The present application (08/486,313) and United States patent application 08/479,796 contain an identical specification, contain identical original claims as filed, and have an identical filing date. Also, both applications received the identical restriction requirements. In both the

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Restriction Requirement in United States patent application 08/479,796, dated June 19, 1996 (see, attached Exhibit 17) and the Restriction Requirement in the present application, dated August 14, 1996 (see, attached Exhibit 18), the claims to remyelination methods (Group III; original claims 16-18) and the claims to transplantation methods (Group VII; original claims 26-27) were restricted to different Groups. Applicants here submit copies of each restriction Requirement.

“A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.” 35 U.S.C. § 121.

For all practical purposes (identical specification, original claims, filing date, and restriction requirement) the present application and United States patent application 08/479,796 are the same original application. After election of the remyelination claims (Group III) or the transplantation claims (Group VII), the present application and United States patent application 08/479,796 are effectively divisional applications. Consistent with the language of 35 U.S.C. § 121, United States patent application 08/479,796 should “not be used as a reference” against the present application.

Also, the nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. *See In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). No such policy concerns are present in this obvious-type double patenting rejection. Had Applicants’ prior representatives filed

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divisional applications on the non-elected claims, rather than simply electing the exact same claims in separate applications, the Examiner could not have made the obvious-type double patenting rejection. However, the scope of Applicants' potential patent protection would have been absolutely identical.

Applicants request that this rejection be withdrawn.

### CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

  
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## EXHIBITS

1. Declaration under 37 C.F.R. 1.132 of Joseph P. Hammang in United States patent application 07/961,813 (11 pp.)
2. Declaration under 37 C.F.R. 1.132 of Joseph P. Hammang in United States patent application 08/479,796 (16 pp.)
3. McKay, *Stem cells in the central nervous system*. 276 Science 66-71 (1997)
4. Baetge, *Neural stem cells for CNS transplantation*. Ann 695 N.Y. Acad. Sci. 285-291 (1993)
5. Hammang *et al.*, Chapter 14, *Transplantation of Epidermal Growth Factor-Responsive Neural Stem Cell Progeny into the Murine Central Nervous System*, in 21 *Methods in Neurosciences*, 281-293 (Flanagan *et al.*, eds., Academic Press, San Diego, 1994)
6. Cattaneo *et al.*, *Non-Virally Mediated Gene Transfer Into Human Central Nervous System Precursor Cells*. 42 Mol. Brain Res. 161-66 (1996)
7. Weiss *et al.*, *Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis*. 16 J. Neurosci. 7599-7609 (1996)
8. Milward *et al.*, *Isolation and transplantation of multipotential populations of epidermal growth factor-responsive, neural progenitor cells from the canine brain*. 50 J. Neurosci. Res. 862-871 (1997)
9. Hammang *et al.*, *Myelination following transplantation of EGF-responsive neural stem cells into a myelin-deficient environment*. 147 (1) Exp Neurol. 84-95 (1997)
10. Winkler *et al.*, *Incorporation and glial differentiation of mouse EGF-responsive neural progenitor cells after transplantation into the embryonic rat brain*, 11(3) Mol. Cell. Neurosci. 99-116 (1998)
11. Zigova & Sanberg, *The rising star of neural stem cell research*. 16 Nature Biotechnol. 1007-1008 (1998)
12. Flax *et al.*, *Engraftable human neural stem cells respond to developmental cues, replace neurons, and express foreign genes*. 16 Nature Biotechnol. 1033-1039 (1998)

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13. Brüstle *et al.*, *Chimeric brains generated by intraventricular transplantation of fetal human brain cells into embryonic rats*. 16 Nature Biotechnol. 1040-1044 (1998)
14. Zhang *et al.*, *Adult brain retains the potential to generate oligodendroglial progenitors with extensive myelination capacity*. 96 Proc. Natl. Acad. Sci. USA 4089-94 (1999)
15. Yandava *et al.*, *"Global" cell replacement is feasible via neural stem cell transplantation: evidence from the dysmyelinated shiverer mouse brain*. 96(12) Proc. Natl. Acad. Sci. 7029-34 (1999).
16. Fricker *et al.*, *Site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain*. 19 J. Neurosci. 5990-6005 (1999).
17. Restriction Requirement in United States patent application 09/486,313 (6/19/96) (5 pp.)
18. Restriction Requirement in the present application (8/24/96) (6 pp.)

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